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QUEEN THOMAS
Printed Name

Queen Thomas
Signature

PATENT APPLICATION IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

The Accompanying Application

Applicants : Hoffmann, James A. and Lu, Jirong

For : **FSH FORMULATION**

Docket No. : X-12383N

PRELIMINARY AMENDMENT

Assistant Commissioner for Patents
Washington, D. C. 20231
Sir:

Applicants are herewith filing a divisional application under 37 C.F.R. 1.53(b) of U.S. Serial No. 09/744,431, which is the United States national stage application of International Application No. PCT/US99/16031, which was filed July 15, 1999. The accompanying application is a copy of the International Application.

Claims 1-61 were filed originally in the International Application. Claims 62-91 were added by Amendment under Article 34(2)(b) in the International Application. In response to the Written Opinion, Applicants canceled Claims 6, 25; 40-44, 60, 68, 69, 89, and 90, leaving Claims 1-5, 7-24, 26-39, 45-59, 61-67, 70-88 and 91 remaining in the application. A preliminary amendment to the United States national application, Ser. No. 09/744,431, filed from the International Application, canceled all claims and requested entry of new Claims 92-140.

Please amend the accompanying application as follows:

In the Title

On page 1, line 1, please delete the title "**FSH AND FSH VARIANT FORMULATIONS, PRODUCTS AND METHODS**" and replace it with the title "**FSH FORMULATION**".

In the Specification

On page 1, lines 4 to 9, please delete the entire paragraph.

Please replace that paragraph with the following:

"This application is a division of U.S. Serial No. 09/744,431, which was filed January 22, 2001 as a United States national application under 35 U.S.C. §371 from the International Application No. PCT/US99/16031, filed July 15, 1999, which claims benefit of U.S. Provisionals 60/093906 filed July 23, 1998, 60/094611 filed July 30, 1998, 60/094767 filed July 31, 1998, 60/098711 filed September 1, 1998, and 60/100696 filed September 17, 1998 each of which application is entirely incorporated herein by reference."

In the Claims

Please cancel all claims, namely, Claims 92-140.

Please add new Claims 141-152.

141. (new) A pharmaceutically acceptable formulation comprising human FSH and benzyl alcohol in an aqueous diluent.

142. (new) The formulation of Claim 141, wherein the human FSH is produced through the use of recombinant DNA technology.

143. (new) The formulation of Claim 142, wherein the human FSH is at a concentration of about 5.0 μg/mL to about 200 μg/mL.

144. (new) The formulation of Claim 143, wherein the human FSH is at a concentration of 50 μg/mL to about 200 μg/mL.

145. (new) The formulation of Claim 144, further comprising sodium phosphate.

146. (new) The formulation of Claim 145, wherein the concentration of benzyl alcohol is 10 mg/mL.

147. (new) The formulation of Claim 143, further comprising sodium phosphate.

148. (new) The formulation of Claim 147, wherein the concentration of benzyl alcohol is 10 mg/mL.

149. (new) The formulation of Claim 142, further comprising sodium phosphate.

150. (new) The formulation of Claim 149, wherein the concentration of benzyl alcohol is 10 mg/mL.

151. (new) The formulation of Claim 141, further comprising sodium phosphate.

152. (new) The formulation of Claim 151, wherein the concentration of benzyl alcohol is 10 mg/mL.

NOTE: Applicants attach at the end of this Preliminary Amendment a sheet containing the new Claims 141-152 for the Examiner's convenience.

Remarks

Amendments in the Specification. The amended title reflects the subject matter encompassed by the new claims. The amended cross-reference paragraph provides an updated listing of related U.S. application data. These amendments do not add new matter.

Amendments in the Claims. Applicants cancel all claims, namely, Claims 92-140, and submit new Claims 141-152. Applicants respectfully request that the new claims be entered.

Applicants reserve the right to file subsequent applications containing one or more of the claims that are hereby canceled.

The new claims are supported throughout the specification of the application as filed. Basis for each new claim is found at least at the place(s) described in the table below.

Claim	Basis
141	Claim 92; Examples 6-7; page 31 line 13 to page 32 line 5.
142	Examples 1-2; page 14, lines 22 to page 15, line 7; page 25 line 1 to page 28, line 4.
143	Page 35, lines 1-10.
144	Page 35, lines 1-10.
145, 147, 149, 151	Page 35, line 31 to page 36, line 9.
146, 148, 150, 152	Examples 6-7 and page 65, line 20 to page 66, line 15.

In summary, Applicants amend the title, the reference to related applications, cancel Claims 92-140, and add new Claims 141-152. The amendments add no new matter and are supported throughout the application.

Respectfully submitted,

James J. Kelley

Eli Lilly and Company
Patent Division/JAH
Lilly Corporate Center
Indianapolis, Indiana 46285

James J. Kelley
Attorney for Applicants
Registration No. 41,888
Phone: 317-277-8110

9 August 2001

New Claims 141-152 added by Preliminary Amendment

141. A pharmaceutically acceptable formulation comprising human FSH and benzyl alcohol in an aqueous diluent.

142. The formulation of Claim 141, wherein the human FSH is produced through the use of recombinant DNA technology.

143. The formulation of Claim 142, wherein the human FSH is at a concentration of about 5.0 µg/mL to about 200 µg/mL.

144. The formulation of Claim 143, wherein the human FSH is at a concentration of 50 µg/mL to about 200 µg/mL.

145. The formulation of Claim 144, further comprising sodium phosphate.

146. The formulation of Claim 145, wherein the concentration of benzyl alcohol is 10 mg/mL.

147. The formulation of Claim 143, further comprising sodium phosphate.

148. The formulation of Claim 147, wherein the concentration of benzyl alcohol is 10 mg/mL.

149. The formulation of Claim 142, further comprising sodium phosphate.

150. The formulation of Claim 149, wherein the concentration of benzyl alcohol is 10 mg/mL.

151. The formulation of Claim 141, further comprising sodium phosphate.

152. The formulation of Claim 151, wherein the concentration of benzyl alcohol is 10 mg/mL.

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SHERRY A. WILSON — Sherry A. Dawson

(Typed or printed name of person mailing application) (Signature of person mailing application)

PATENT APPLICATION

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant Docket:	X-12383M
International Application No.:	PCT/US99/16031
Applicant(s):	ELI LILLY AND COMPANY
Earliest Priority Date:	23 July 1998 (23.07.98)
International Filing Date:	15 July 1999 (15.07.99)
Invention:	FSH AND FSH VARIANT FORMULATIONS, PRODUCTS AND METHODS

AMENDMENT UNDER ARTICLE 34(2)(b)

Attn: IPEA/US
Assistant Commissioner for Patents
Box PCT
Washington, D. C. 20231

Dear Sir/Madam:

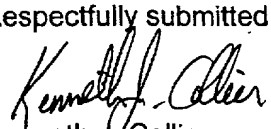
A PCT Demand under Article 31 of the Patent Cooperation Treaty is submitted herewith for the above-captioned application. Upon review of the application, Applicant noted the need for additional claims to identify and distinctly claim that which Applicant believes to be their invention. Accordingly, Applicant submits herewith the following Amendment Under Article 34(2)(b). Attached are replacement pages 78-83 to replace pageS 78-79 of the application as originally filed.

Remarks

Claims 62-91 have been added. Support for this amendment is found throughout the specification and in particular in the Summary of the Invention (pages 6-8), the Detailed Description (pages 8 and 31-41), and in Examples 1-9 (pages 41-66) as originally filed.

In accordance with Article 34(2)(b), the amendments do not go beyond the disclosure of the international application as filed.

Respectfully submitted,



Kenneth J. Collier
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Eli Lilly and Company
Patent Division/DC 1104/KJC
Lilly Corporate Center
Indianapolis, Indiana 46285

February 17, 2000

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Date of Deposit: December 22, 2000 (12-22-00)
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JEFFREY A. WILSON
(Typed or printed name of person mailing application)

(Signature of person mailing application)

PATENT APPLICATION

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant Docket:	X-12383M
International Application No.:	PCT/US99/16031
Applicant(s):	ELI LILLY AND COMPANY
Earliest Priority Date:	23 July 1998 (23.07.98)
International Filing Date:	15 July 1999 (15.07.99)
Invention:	FSH AND FSH VARIANT FORMULATIONS, PRODUCTS AND METHODS

LETTER ACCOMPANYING AMENDMENT UNDER ARTICLE 34(2)(b)

Attn: IPEA/US
Assistant Commissioner for Patents
Box PCT
Washington, D. C. 20231

Dear Sir/Madam:

Attached are replacement pages 78-83 for the application in this matter, which was mailed on July 15, 1999.

In the Claims

Claims 62-91 have been added. Support for this amendment is found throughout the specification and in particular in the Summary of the Invention (pages 6-8), the Detailed Description (pages 8 and 31-41), and in Examples 1-9 (pages 41-66) as originally filed.

No amendment goes beyond the disclosure in the international application as filed.

Applicant respectfully requests that the International Preliminary Examining Authority start the international preliminary examination taking into account the replacement sheets filed under Article 19 on December 10, 1999 and the

replacement sheets submitted herewith. Applicant requests the issuance of a favorable Preliminary Examination Report or, in the alternative, an early Written Opinion.

Respectfully submitted,

Kenneth J. Collier

Kenneth J. Collier
Attorney for Applicant
Registration No. 34,982
Phone: 317-433-6433

Eli Lilly and Company
Patent Division/DC 1104/KJC
Lilly Corporate Center
Indianapolis, Indiana 46285

February 17, 2000

APDVQDCPECTLQENPFFSQPGAPILQCMGCCFSRAYPTPLRSKKTMLVQKNVTSE
STCCVAKSYNRVTVMGGFKVENHTACHCSTCYYHKS

β-subunit: (SEQ ID NO:13)

NSCELTNITIAIEKEECRFCISINTTWCAGYCYTRDLVYKDPARPKIQKTCTFKE
LVYETVRVPGCAHHADSLYTYPVATQCHCGKCDSDSTDCTVRGLGPSYCSFGEMK

62. A formulation comprising a FSH variant and a pharmaceutically acceptable excipient.

63. A formulation comprising a FSH variant, containing an alpha and beta subunit, with a preservative selected from the group consisting of phenol, m-cresol, p-cresol, o-cresol, chlorocresol, benzyl alcohol, alkylparaben (methyl, ethyl, propyl, butyl and the like), benzalkonium chloride, benzethonium chloride, sodium dehydroacetate and thimerosal, or mixtures thereof in an aqueous diluent.

64. A formulation of Claim 63, wherein the preservative is phenol, m-cresol, chlorocresol, or a mixture thereof.

65. A formulation of Claim 63, wherein the FSH variant is about 1.0 μg/ml to about 50 mg/ml.

66. A formulation of Claim 63, further comprising an isotonicity agent.

67. A formulation of Claim 63, further comprising a physiologically acceptable buffer.

68. A formulation comprising a FSH variant lyophilized in a first vial, and a second vial containing a preservative selected from the group consisting of phenol, m-cresol, p-cresol, o-cresol, chlorocresol, benzyl alcohol, alkylparaben (methyl, ethyl, propyl, butyl and the like), benzalkonium chloride, benzethonium chloride, sodium dehydroacetate and thimerosal, or mixtures thereof in an aqueous diluent.

69. A formulation of Claim 68, wherein a FSH variant and preservative are further put into solution.

70. A formulation of Claim 63 or 68, wherein a FSH variant is at least one compound selected from the group consisting of:

(f):α-subunit:(SEQ ID NO:5)
APDVQDCPECTLQENPFFSQPGAPILQCMGCCFSRAYPTPLRSKKTMLVQKNVTSE
STCCVAKSYNRVTVMGGFKVENHTACHCSTCYYHKS
β-subunit:(SEQ ID NO:11)
NSCELTNITIAIEKEECRFCISINTTWCAGYCYTRDLVYKDPARPKIQKTCTFKEL
VYETVRVPGCAHHADSLYTYPVATQCHCGKCDSDSTDCTVRGLGPSYCSFGE

(g):α-subunit:(SEQ ID NO:5)
APDVQDCPECTLQENPFFSQPGAPILQCMGCCFSRAYPTPLRSKKTMLVQKNVTSE
STCCVAKSYNRVTVMGGFKVENHTACHCSTCYYHKS
β-subunit:(SEQ ID NO:12)
NSCELTNITIAIEKEECRFCISINTTWCAGYCYTRDLVYKDPARPKIQKTCTFKEL
VYETVRVPGCAHHADSLYTYPVATQCHCGKCDSDSTDCTVRGLGPSYCSFGEM

(h):α-subunit:(SEQ ID NO:5)
APDVQDCPECTLQENPFFSQPGAPILQCMGCCFSRAYPTPLRSKKTMLVQKNVTSE
STCCVAKSYNRVTVMGGFKVENHTACHCSTCYYHKS
β-subunit:(SEQ ID NO:13)
NSCELTNITIAIEKEECRFCISINTTWCAGYCYTRDLVYKDPARPKIQKTCTFKEL
VYETVRVPGCAHHADSLYTYPVATQCHCGKCDSDSTDCTVRGLGPSYCSFGEMK

71. A method of treating infertility which comprises administering to a patient in need thereof a formulation according to Claim 62, 63, or 70.

72. A method of Claim 71, wherein said patient is selected from the group consisting of a human, sheep, cow, pig, horse, or rabbit.

73. A process for preparing a preserved solution formulation of a FSH variant, containing an alpha and beta subunit, which comprises admixing said FSH variant and a preservative selected from the group consisting of phenol, m-cresol, p-cresol, o-cresol, chlorocresol, benzyl alcohol, alkylparaben (methyl, ethyl, propyl, butyl and the like), benzalkonium chloride, benzethonium chloride, sodium dehydroacetate and thimerosal, or mixtures thereof, in an aqueous diluent.

74. An article of manufacture comprising a FSH variant in a container.

75. The article of manufacture of Claim 74, wherein said container is a glass container.

76. The article of manufacture of Claim 74, wherein said container is a blister pack.

77. The article of manufacture of Claim 74, wherein said container is a pen-injector device.

78. A method of treating infertility in a patient, which comprises administering to a patient in need thereof a preserved solution of a FSH variant, containing an alpha and beta subunit, said solution being suitable for administration over a period of 24 hours or greater.

79. A formulation comprising a first vial containing a a FSH variant containing an alpha and beta subunit, and a second vial containing phosphate buffer containing saline or a salt.

80. A process for preparing a stable solution formulation of a FSH variant, containing an alpha and beta subunit, which comprises admixing a FSH variant with a phosphate buffer containing saline or a salt.

81. Use of a formulation of claim 62 or 63 for treating infertility in a patient in need thereof.

82. Use of a formulation of claim 62 or 63 wherein said patient is selected from the group consisting of a human, sheep, cow, pig, horse, or rabbit.

83. A process of producing a formulation comprising admixing a FSH variant, containing an alpha and beta subunit, and a preservative selected from the group consisting of phenol, m-cresol, p-cresol, o-cresol, chlorocresol, benzyl alcohol, alkylparaben (methyl, ethyl, propyl, butyl and the like), benzalkonium chloride, benzethonium chloride, sodium dehydroacetate and thimerosal, or mixtures thereof in an aqueous diluent.

84. A process of producing a stable formulation comprising admixing at least a FSH variant, containing an

alpha and beta subunit, and a phosphate buffer containing saline or a salt.

85. A process of Claim 83, wherein the preservative is phenol, m-cresol, chlorocresol, or a mixture thereof.

86. A process according to any of Claims 83-84, wherein the concentration of FSH or a FSH variant is about 1.0 μg/ml to about 50 mg/ml.

87. A process according to any of Claims 83-84, further admixing an isotonicity agent.

88. A process of Claim 83-84, further admixing a physiologically acceptable buffer.

89. A process comprising preparing a FSH variant lyophilized in a first vial, and preparing a second vial containing a preservative selected from the group consisting of phenol, m-cresol, p-cresol, o-cresol, chlorocresol, benzyl alcohol, alkylparaben (methyl, ethyl, propyl, butyl and the like), benzalkonium chloride, benzethonium chloride, sodium dehydroacetate and thimerosal, or mixtures thereof in an aqueous diluent.

90. A process of Claim 89, wherein said FSH or a FSH variant and preservative are further put into solution.

91. A process according to any of claims 84-85, wherein FSH variant is at least one compound selected from the group consisting of:

(f):α-subunit:(SEQ ID NO:5)

APDVQDCPECTLQENPFFSQPGAPILQCMGCCFSRAYPTPLRSKKTMLVQKNVTSE
STCCVAKSYNRVTVMGGFKVENHTACHCSTCYYHKS

β-subunit:(SEQ ID NO:11)

NSCELTNITIAIEKEECRFCISINTTWCAGYCYTRDLVYKDPARPKIQKTCTFKEL
VYETVRVPGCAHHADSLYTYPVATQCHCGKCDSDSTDCTVRGLGPSYCSFGE

(g):α-subunit:(SEQ ID NO:5)

APDVQDCPECTLQENPFFSQPGAPILQCMGCCFSRAYPTPLRSKKTMLVQKNVTSE
STCCVAKSYNRVTVMGGFKVENHTACHCSTCYYHKS

β-subunit:(SEQ ID NO:12)

NSCELTNITIAIEKEECRFCISINTTWCAGYCYTRDLVYKDPARPKIQKTCTFKEL
VYETVRVPGCAHHADSLYTYPVATQCHCGKCDSDSTDCTVRGLGPSYCSFGEM

(h): α-subunit: (SEQ ID NO:5)

APDVQDCPECTLQENPFFSQPGAPILQCMGCCFSRAYPTPLRSKKTMLVQKNVTSE
STCCVAKSYNRVTVMGGFKVENHTACHCSTCYYHKS

β-subunit: (SEQ ID NO:13)

NSCELTNITIAIEKEECRFCISINTTWCAGYCYTRDLVYKDPARPKIQKTCTFKEL
VYETVRVPGCAHHADSLYTYPVATQCHCGKCDSDSTDCTVRGLGPSYCSFGEMK